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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/787,144 | 07/16/2001 | Nassar Chegini | G0651/7026 | 6136 |

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| EXAMINER | |
|---|---|
| HADDAD, MAHER M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | 4 |

DATE MAILED: 07/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/787,144 | CHEGINI ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- Th MAILING DATE of this communication app ars on the cov r sh t with the correspondenc address --*

**Period for R ply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on 6/16/03

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-14* is/are pending in the application.

4a) Of the above claim(s) *3-10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. The Art Unit location and the examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Maher Haddad, Art Unit 1644, Technology Center 1600.

2. Applicant's amendment, filed 6/16/03 (Paper No. 9), is acknowledged.

3. Claims 1 and 3-14 are pending.

4. Claims 3-10 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

5. Claims 1 and 11-14 are under consideration as they read on a method for the prevention of remediation of surgical adhesions comprising treating a patient with a therapeutic formulation comprising TIMP-1 antibodies.

6. In view of the amendment filed on 6/16/03 (Paper No. 9), only the following rejection is remained.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

8. Claims 1 and 11-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action, paper No. 8, mailed 1/13/03.

Applicant's arguments, filed 6/16/03 (Paper No. 9), have been fully considered, but have not been found convincing.

As noted previously in paper No. 8, no *in vitro* or *in vivo* exemplification in the specification is drawn to the efficacy of the claimed antibodies for the prevention or remediation of surgical adhesions. While a correlation between the levels of TIMP-1 in the peritoneal cavity and the tendency of the patients to develop adhesions may provide an indication that particular compounds/compositions are appropriate to target for *further experimental consideration.*

Applicant's disclosure does not appear to have provided the skilled artisan with sufficient guidance and support as how to extrapolate the development of effective *in vivo* human therapeutic methods, commensurate in scope with the claimed invention.

In addition, Kahan states that, at the time of the invention, "no in vitro immune assay predicts or correlates with in vivo immunosuppressive efficacy; hence, there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in vitro systems to in vivo conditions" (Curr. Opin. Immuno. 4:553:560, 1992; see entire document, particularly page 558, column 2) making the in vivo efficacy of untested TIMP-1 antibody unpredictable. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the absence of a specific and detailed description in Applicant's specification of how to effectively use the methods as claimed, and absence of working examples providing evidence which is reasonably predictive that the claimed methods are effective for in vivo use, and the lack of predictability in the art at the time the invention was made, an undue amount of experimentation would be required to practice the claimed methods with a reasonable expectation of success.

Applicant argues that using antibody for therapeutic treatment purposes has been well known and there is a high level of skill in the art at the time the application was filed. Applicant directed the Examiner's attention to U.S Patent No
4,731,245,
5,110,738,
5,487,892,
5,545,403,
5,616,32? and
5,762,923

While `245 patent is drawn to an in vitro assay for detecting a female reproductive tract disorder in a subject comprising detecting the expression of a cytokine of IL-13 and IL-15 in the sample, and has no relation to the in vivo use of antibody for therapeutic treatment purposes.

The ` 738 patent is drawn to a Hybridoma and has no relation to the in vivo use of antibody for therapeutic treatment purposes.

The `892 patent is drawn to method for reducing the rate of fibrin deposition in a human, comprising administering the fibrin-specific monoclonal antibody MH-1 produced by hybridoma ATCC 9739, or an antibody that binds to the same epitope as monoclonal antibody MH-1. The `403 patent is drawn to a method for treating a human suffering from a disease or disorder comprising administering a whole glycosylated recombinant human chimeric or CDR-grafted or bispecific antibody effective in treating said disease or disorder in said human, wherein the improvement comprises an antibody glycosylated by a chinese hamster ovary cell.

Examiner acknowledges that the `892 and `403 patents do provide some support that antibody may be used in therapeutic treatment purposes in certain situations. However neither `892 patent nor `403 patent used TIMP-1 antibodies *in vivo* or prevent surgical adhesions. Thus it is unclear how administering anti-TIMP-1 in vivo would prevent surgical adhesions.

Regarding patent 5,616,32?, it is unclear what patent is recited.

The `923 patent is drawn to a human serum albumin-free aqueous interferon composition which comprises about 10.sup.6 -10.sup.8 IU/ml of interferon-alpha dissolved in water with a non-ionic detergent and 8 to about 20 mg/ml of benzyl alcohol which composition contains an amount of buffer which provides a pH of 4.5 to 6.0 and is characterized by absence of human serum albumin and has no relation to the use of antibody for therapeutic treatment purposes.

Applicant submits that the present application has taught the correlation of the level of TIMP and the tendency of forming adhesions. The prior art has taught methods of treatment with an antibody. Applicant concluded that one of ordinary skill in the art would have been able to determine an appropriate dosage of the therapeutic formulation of the present invention, an appropriate route of administration, and manner of evaluating its efficacy in patients.

However, the current state of the art in antibody therapeutics and the predictability of treatment efficacy is complicated by the potential for antibody interactions with irrelevant or completing epitopes, Fc region engagement, reduced half life of antibody fragments, and immune response to the therapeutic antibodies (see Ward et al, pages 167-171, 1994 "consideration related to use of blocking antibodies"). On the basis of the disclosed correlation of the level of TIMP and the tendency of forming adhesion observation alone, applicant concludes that the scope of the antibody against TIMP-1 encompassed by the claimed invention can have biological activity to prevent the surgical adhesions and be provided as pharmaceutical compositions to subjects including human to effectively prevent surgical adhesions.

Applicant submits that a patent need not teach, and preferably omits, what is well known in the art. Applicant further submits that considering the high level of skill in the art and the sufficient teachings in the prior art, the factor of "the amount of guidance or direction" also favors that the present invention is enabled to a person of ordinary skill.

While the Examiner agree with Applicant statement that a patent need not teach what is well known in the art. However, the methods of preventing surgical adhesions using anti-TIMP-1 antibodies are not known in the art and considered an essential element of the claimed invention. Therefore, the amount of guidance and direction required is high to enable a person of ordinary skill in the art to practice the present invention.

Applicant argues that "the amount of experimentation required," is only one factor that must be considered. Time and difficulty of experiments are not determinative if they are merely routine. Applicant argues that since determining the dosage and efficacy of the present invention is

merely routine, lacking in vivo or in vitro example should not be determinative to the enablement of the present invention.

However, this argument would be acceptable if the general conditions of a claim are disclosed in the prior art, then discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. In the instant application, the method of prevention or remediation of surgical adhesions using anti-TIMP-1 antibodies is not disclosed in the prior art.

9. No claim allowed

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
July 25, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
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